Re: Zinc Supplement Use and Risk of Prostate Cancer

Although the etiology of prostate cancer is still virtually unknown, some epidemiologic, experimental, and dietary supplement studies have provided evidence of a protective role for zinc in the development and progression of prostate malignancy. However, results of other studies have suggested that high intraprostatic zinc levels may increase prostate cancer risk. The recent study in the Journal by Leitzmann et al. *(1)* amplifies this concern by reporting that an increased risk of advanced prostate cancer is associated with zinc intake of greater than 100 mg/day, as well as with the long-term (i.e., >10 years) use of supplemental zinc. However, no strong evidence could be identified in support of specific mechanisms for the observed associations. We suggest that the presence of cadmium in some zinc supplements could contribute to the observed association between zinc supplement use and prostate cancer risk *(2)*.

Contrary to the physiologic and potentially beneficial effects of zinc, cadmium has been implicated epidemiologically and experimentally in the etiology of prostate cancer *(3)*. Cadmium induces conformational changes in p53, presumably by replacing zinc atoms that normally bind this protein, and impairs the DNA-binding activity of p53 and the subsequent induction of cell cycle arrest after DNA damage *(4)*. Malignant transformation of human prostate epithelial cells *in vitro* was associated with exposure to a cadmium concentration at the low end of the concentration range found in human prostates of men who do not have occupational cadmium exposure *(5)*.

Zinc and cadmium have very similar chemical properties and are invariably found together in nature. All commercially available zinc supplements that we analyzed *(2)* contained detectable levels of cadmium; however, the amounts varied by almost 40-fold when based on a fixed amount of zinc (e.g., 15 mg, the recommended daily allowance for zinc). We estimate that consumption of approximately 140 mg/day of zinc [the median daily level of zinc supplement intake among the high-intake group studied by Leitzmann et al. *(1)*] in the zinc supplement that we found contains the highest cadmium-to-zinc ratio would yield a cadmium dose of approximately 19 μg/day. This dose is nearly double the total mean daily exposure to cadmium from foods, excluding shellfish, as estimated in the U.S. Food and Drug Administration Total Diet Study (i.e., 10 μg cadmium/person/day). For members of the general public that are not occupationally exposed to cadmium, food is the major route of cadmium uptake. Humans accumulate cadmium with age; the biologic half-life of cadmium is on the order of decades. It has been suggested that even small repeated low doses of cadmium could accumulate in the body and mimic the activities of zinc, leading to the adverse effects on prostate health associated with cadmium intake *(5)*.

Our results suggest that zinc supplements with relatively low cadmium levels can and should be produced [e.g., supplements containing the gluconate form of zinc uniformly had lower levels of cadmium than those containing zinc sulfate or zinc as an amino acid chelate *(2)*]. The risks and benefits associated with dietary supplements deserve further study because dietary supplementation could be an inexpensive and easy way to prevent various malignancies and other disorders. However, it is necessary to use caution when adopting dietary supplement regimens. Not only can there be undetected or unknown toxic chemicals in such supplements, but the action of pure dietary components such as zinc at pharmacologic doses does not always produce the expected effects. A further example of this is the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Trial, in which an unanticipated and undesirable increase in lung cancers was observed among the cigarette smokers given pharmacologic doses of beta-carotene *(6)*. Indeed, one could also ask of zinc supplements: are they friend or foe?

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RESPONSE

Krone and Harms suggest that the apparent adverse effect of zinc supplements on advanced prostate cancer risk is due to contamination of zinc supplements by cadmium. Cadmium exposure

has not been consistently associated with prostate cancer incidence or mortality in epidemiologic studies of cadmium exposure determined by dietary, environmental, blood, or toenail assessment *(1–3).* However, because cadmium is a known carcinogen *(4),* the presence of cadmium in zinc supplements is of potential concern.

Data regarding the cadmium content of zinc supplements are limited to one study *(5).* That study found that single-mineral, zinc-only supplements contained trace amounts of cadmium (0.049 μg cadmium/15 mg zinc). By contrast, multi-mineral products containing a variety of other minerals in addition to zinc had more than 20 times the amount of cadmium (1.06 μg cadmium/15 mg zinc). As suggested by the authors, one possible reason for the increased cadmium content in multi-mineral supplements is their lower degree of purity than single-mineral products *(5).* Another possibility is that high cadmium amounts contained in multi-mineral supplements may be attributable to the presence of minerals other than zinc. For example, one study found markedly increased cadmium levels in calcium supplements *(6).*

Our study lacks data to rule out the possibility that zinc supplement use is positively linked to advanced prostate cancer because of cadmium contamination of supplements. However, excluding subjects who used multivitamin supplements and limiting the analysis to men using zinc-only supplements did not affect the observed positive association between zinc supplement use and risk of advanced prostate cancer in our study. Hence, it is unlikely that the associations we observed can be explained by a higher degree of impurity (i.e., higher cadmium content) of multi-mineral supplements. Notwithstanding, we agree with Krone and Harms that because certain types of dietary supplements may contain nonessential, and potentially harmful, trace elements, further research is warranted to determine the presence of such contaminants in supplements. Such studies may help clarify the risk–benefit trade-offs associated with dietary supplement use.

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